

II. REMARKS

Claims 36-49 and 62-83 were pending. In this Amendment, claims 36, 39, 43, 46, 62 and 68 are amended, and claims 37, 44, 63, 69 and 74-83 are canceled. Claims 36, 38-43, 45-62, 64-68 and 70-73 are presented for reconsideration.

The amendments to the claims are supported, for example, by the prior claims and the specification, for example on page 2, line 30 through page 3, line 3, and page 5, lines 7-10. No new matter has been added.

Claims 36-49 and 62-83 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Breivik et al. (U.S. Patent No. 5,502,077) in view of Harrison's Principals of Internal Medicine, 13th Edition, for the reasons set forth on pages 7-9 of the Office Action dated March 9, 2007.

Breivik et al. '077 is relied upon as teaching that fatty acid compositions having at least 80% by weight of omega-3 fatty acids can be used for the treatment or prevention of multiple risk factors for cardiovascular diseases. Harrison's is merely added to support the notion that the risk factors identified by Breivik et al. '077 are known to be associated with myocardial infarction. Referring to Breivik et al. '077 in the prior Office Action, the Examiner indicated:

[O]n its face, it is clearly reasonable to hold the belief that an agent which reduces the risk of an event from occurring would reduce the incidence of that event.... If such risk factors [for cardiovascular diseases] become non-existent through an efficacious regimen of omega-3 fatty acid administration, a patient would no longer have those factors which predispose him/her to suffer a cardiovascular event.

March 9, 2007 Office Action, pages 8-9 (emphasis added).

The present invention is directed to reducing the incidence of mortality or sudden death caused by the reoccurrence of cardiovascular events in a patient who has survived a myocardial infarction, by administering to such a patient a medicament containing essential fatty acids at a dosage of about 0.7g to about 1.5g daily, or dosage forms containing about 1g of oil comprising omega-3 fatty acids. The content of EPA+DHA in the medicament or dosage forms is from about 60 to about 100% by weight. As discussed in detail below, one of ordinary skill in the art would not have expected such a relatively low dosing regimen to reduce the incidence of mortality or sudden death caused by the reoccurrence of cardiovascular events, because such a dosing regimen has been shown in the art to have no clinically significant effect on blood lipid levels, which are risk factors for cardiovascular diseases. Yet, surprisingly and contrary to the logic used by the Examiner, such a dosing regimen does reduce the incidence of mortality or sudden death caused by the reoccurrence of cardiovascular events.

The commercial embodiment of the Breivik et al. '077 patent is a product known as LOVAZA™. See the "Orange Book" print out for LOVAZA™ listing the Breivik et al. '077 patent, attached as Attachment 1. LOVAZA™ is supplied as a 1 gram capsule containing approximately 84% by weight of EPA+DHA (approximately 465 mg of EPA and approximately 375 mg of DHA). LOVAZA™ is approved for the treatment of hypertriglyceridemia, a risk factor for cardiovascular diseases, at an oral dose of 4g/day. See the attached Prescribing Information for LOVAZA™, attached as Attachment 2. Following the logic of the Examiner above, one of ordinary skill in the art would

therefore expect a dose of 4g/day to have a significant effect on the reduction of cardiovascular events. However, the dose range of the present invention centers around 1g daily, or about 25% of the daily dose of LOVAZA™. As noted in the attached Declaration by Dr. Benjamin Levinson, the 1g/day dose has been shown in the art to have no clinically significant effect on blood lipid levels. Therefore, again following the logic of the Examiner above, one of ordinary skill in the art would likewise expect a dose of 1g/day to have no significant effect on the reduction of cardiovascular events. Surprisingly, this is not the case.

The GISSI-Prevenzione trial, attached as Attachment 2 to Dr. Levinson's Declaration, studied over 11,000 patients who previously suffered a myocardial infarction, to monitor the reoccurrence of cardiovascular events. Patients in the "omega-3 fatty acids" group were administered omega-3 polyunsaturated fatty acids at a dosage of 1g daily.¹ See the Summary under "Methods," page 447. The study monitored changes in blood lipid concentrations and looked at several efficacy endpoints, including the occurrences of cardiovascular deaths and sudden death from a cardiovascular event. See Table 3, page 450.

As noted on page 451 of the article, compared with baseline values, there were no clinically important changes in the blood cholesterol profile (total cholesterol, HDL cholesterol, or LDL cholesterol) after 6 months, in patients administered 1g/day of omega-3 fatty acids. Based on the teachings of Breivik et al. '077, if there were no clinically important changes in the blood lipid profile, one of ordinary skill in the art would

¹ The 1g dosage forms contained 850-882 mg of EPA+DHA. See page 448.

not expect there to be a significant effect in the reduction of the occurrence of cardiovascular events. As noted in Dr. Levinson's Declaration, this (erroneous) belief is also supported by the application of the well-known Framingham and PROCAM risk models for cardiovascular events. The data generated from both of these models strongly imply a lack of clinical benefit of 1g/day administration of omega-3 fatty acids in reducing the occurrence of cardiovascular events, based on the changes in blood lipid concentrations.

This predicted lack of clinical benefit is in stark contrast to the highly statistically significant reduction in cardiovascular events achieved in the GISSI-Prevenzione study. The reoccurrence of cardiovascular events is reported on page 451 of the *Lancet* paper. In the omega-3 group, there was a highly significant 30% decrease in cardiovascular deaths ($p=0.0242$) and a highly significant 45% decrease in sudden death ($p=0.010$) with the 1g/day administration of omega-3 fatty acids. Based on the teachings of Breivik et al. '077, one of ordinary skill in the art would not have expected a daily dose of essential fatty acids that has been reported to have no clinically significant benefit in normalizing blood lipid levels to have a significant effect on the reduction of the reoccurrence of cardiovascular events.

The claims in the present application have been limited to center around the methods utilized in the GISSI-Prevenzione study; that is, the administration of 1g/day of omega-3 fatty acids containing 850-882 mg of EPA+DHA. Specifically, the claims have been limited to a dosage of about 0.7g to about 1.5g daily, or dosage forms containing about 1g of oil comprising omega-3 fatty acids, and a content of EPA+DHA from about

60 to about 100% by weight. Applicant submits that the combination of Breivik et al. '077 and Harrison's does not disclose or suggest that a comparatively low dose of omega-3 fatty acids, which dose has been shown in the art to have no clinically significant benefit in normalizing blood lipid levels, could have a significant effect on the reduction of the reoccurrence of cardiovascular events. Applicant respectfully submits that the present invention is patentable over the combination of Breivik et al. '077 and Harrison's.

III. CONCLUSION

Applicant submits that the application is in condition for allowance and requests favorable action thereon.

In the event that this paper is not timely filed, Applicant requests an appropriate extension of time. The fee for such an extension or any other fee deficiency may be charged, or any overpayment with respect to this paper may be credited, to Deposit Account Number 01-2300, referencing Attorney Docket Number **026392-00095**.

Respectfully submitted,

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Search results from the "OB_Rx" table for query on "021654."

| | |
|---|---------------------------|
| Active Ingredient: | OMEGA-3-ACID ETHYL ESTERS |
| Dosage Form;Route: | CAPSULE; ORAL |
| Proprietary Name: | LOVAZA |
| Applicant: | RELIANT PHARMS INC |
| Strength: | 1GM |
| Application Number: | 021654 |
| Product Number: | 001 |
| Approval Date: | Nov 10, 2004 |
| Reference Listed Drug | Yes |
| RX/OTC/DISCN: | RX |
| TE Code: | |
| Patent and Exclusivity Info for this product: | View |

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Orange Book Data Updated Through September, 2007

Patent and Generic Drug Product Data Last Updated: October 25, 2007

Patent and Exclusivity Search Results from query on Appl No 021654 Product 001 in the OB_Rx list.**Patent Data**

| Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code |
|---------------|---------|-----------|-------------------|----------------------|--------------------|-----------------|
| <u>021654</u> | 001 | 5502077 | MAR 26,2013 | Y | | <u>U-822</u> |
| <u>021654</u> | 001 | 5656667 | AUG 27,2018 | Y | Y | <u>U-822</u> |
| <u>021654</u> | 001 | 5698594 | AUG 04,2009 | Y | | <u>U-822</u> |

Exclusivity Data

| Appl No | Prod No | Exclusivity Code | Exclusivity Expiration |
|---------------|---------|------------------|------------------------|
| <u>021654</u> | 001 | <u>M-64</u> | <u>JUN 12,2010</u> |
| <u>021654</u> | 001 | <u>NCE</u> | <u>NOV 10,2009</u> |

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.
5. U.S. Patent Nos. RE 36481 and RE 36520 were relisted for Zocor (NDA 19-766) pursuant to the decision and related order in *Ranbaxy Labs. v. Leavitt*, No. 05-1838 (D.D.C. April 30, 2006). The '481 and '520 patents remained listed in Approved Drug Products with Therapeutic Equivalence Evaluations until any applicable periods of exclusivity pursuant to section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act were triggered and run. For additional information on this matter, please refer to Docket Nos. 2005P-0008 and 2005P-0046. Patents were subsequently delisted in the December 2006 Orange Book update as the exclusivity periods have triggered and run to expiration.
6. Patent number 4904769 listed on all products of NDA 20482 Precose (Acarbose) was requested to be delisted by the sponsor on 4/16/2007. This patent has remained listed because, under Section 505(j)(5)(D)(i) of the Act, a first applicant may retain eligibility for 180-day exclusivity based on a paragraph IV certification to this patent for a certain period.

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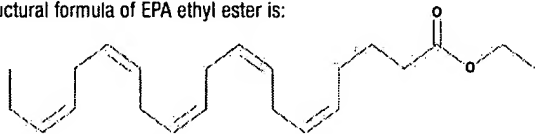
LOVAZA™

(omega-3-acid ethyl esters) Capsules

DESCRIPTION

Lovaza, a lipid-regulating agent, is supplied as a liquid-filled gel capsule for oral administration. Each one gram capsule of Lovaza (omega-3-acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA - approximately 465 mg) and docosahexaenoic acid (DHA - approximately 375 mg).

The structural formula of EPA ethyl ester is:



The empirical formula of EPA ethyl ester is $C_{22}H_{34}O_2$, and the molecular weight of EPA ethyl ester is 330.51.

The structural formula of DHA ethyl ester is:



The empirical formula of DHA ethyl ester is $C_{24}H_{36}O_2$, and the molecular weight of DHA ethyl ester is 356.55.

Lovaza capsules also contain the following inactive ingredients: 4 mg α -tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil), and gelatin, glycerol, and purified water (components of the capsule shell).

CLINICAL PHARMACOLOGY

Mechanism of Action:

The mechanism of action of Lovaza is not completely understood. Potential mechanisms of action include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal β -oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. Lovaza may reduce the synthesis of triglycerides (TGs) in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.

Pharmacokinetic and Bioavailability Studies:

In healthy volunteers and in patients with hypertriglyceridemia (HTG), EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters (Lovaza) induced significant, dose-dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters. Uptake of EPA and DHA into serum phospholipids in subjects treated with Lovaza was independent of age (<49 years vs. \geq 49 years). Females tended to have more uptake of EPA into serum phospholipids than males. Pharmacokinetic data on Lovaza in children are not available.

Drug Interactions:

Cytochrome P450-Dependent Monooxygenase Activities: The effect of a mixture of free fatty acids (FFA), EPA/DHA and their FFA-albumin conjugate on cytochrome P450-dependent monooxygenase activities was assessed in human liver microsomes. At the 23 μ M concentration, FFA resulted in a less than 32% inhibition of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A. At the 23 μ M concentration, the FFA-albumin conjugate resulted in a less than 20% inhibition of CYP2A6, 2C19, 2D6, and 3A, with a 68% inhibition being seen for CYP2E1. Since the free forms of the EPA and DHA are undetectable in the circulation (<1 μ M), clinically significant drug-drug interactions due to inhibition of P450 mediated metabolism EPA/DHA combinations are not expected in humans.

CLINICAL STUDIES

High Triglycerides: Add-on to HMG-CoA reductase inhibitor therapy

The effects of Lovaza 4 g per day as add-on therapy to treatment with simvastatin were evaluated in a randomized, placebo-controlled, double-blind, parallel-group study of 254 adult patients (122 on Lovaza and 132 on placebo) with persistent high triglycerides (200 - 499 mg/dL) despite simvastatin therapy (Table 1). Patients were treated with open-label simvastatin 40 mg per day for 8 weeks prior to randomization to control their LDL-C to no greater than 10% above NCEP ATP III goal and remained on this dose throughout the study. Following the 8 weeks of open-label treatment with simvastatin, patients were randomized to either Lovaza 4 g per day or placebo for an additional 8 weeks with simvastatin co-therapy. The median baseline triglyceride and LDL-C levels in these patients were 268 mg/dL and 89 mg/dL, respectively. Median baseline non-HDL-C and HDL-C levels were 138 mg/dL and 45 mg/dL, respectively.

The changes in the major lipoprotein lipid parameters for the Lovaza plus simvastatin and the placebo plus simvastatin groups are shown in Table 1.

Table 1: Response to the Addition of LOVAZA 4 g per day to On-going Simvastatin 40 mg per day Therapy in Patients with High Triglycerides (200 to 499 mg/dL)

| Parameter | LOVAZA + Simvastatin N=122 | | | Placebo + Simvastatin N=132 | | | Difference | P-Value |
|-----------|-------------------------------|-----|-----------------|--------------------------------|-----|-----------------|------------|---------|
| | BL | EOT | Median % Change | BL | EOT | Median % Change | | |
| Non-HDL-C | 137 | 123 | -9.0 | 141 | 134 | -2.2 | -6.8 | <0.0001 |
| TG | 268 | 182 | -29.5 | 271 | 260 | -6.3 | -23.2 | <0.0001 |
| TC | 184 | 172 | -4.8 | 184 | 178 | -1.7 | -3.1 | <0.05 |
| VLDL-C | 52 | 37 | -27.5 | 52 | 49 | -7.2 | -20.3 | <0.05 |
| Apo-B | 86 | 80 | -4.2 | 87 | 85 | -1.9 | -2.3 | <0.05 |
| HDL-C | 46 | 48 | +3.4 | 43 | 44 | +1.2 | +4.6 | <0.05 |
| LDL-C | 91 | 88 | +0.7 | 88 | 85 | -2.8 | +3.5 | =0.05 |

BL = Baseline (mg/dL); EOT = End of Treatment (mg/dL); Median % Change = Median Percent Change from Baseline; Difference = LOVAZA Median % Change - Placebo Median % Change

LOVAZA™

(omega-3-acid ethyl esters) Capsules

Lovaza 4 g per day significantly reduced non-HDL-C, TG, TC, VLDL-C, and Apo-B levels and increased HDL-C and LDL-C from baseline relative to placebo.

Very High Triglycerides: Monotherapy

The effects of Lovaza 4 g per day were assessed in two randomized, placebo-controlled, double-blind, parallel-group studies of 84 adult patients (42 on Lovaza, 42 on placebo) with very high triglyceride levels (Table 2). Patients whose baseline triglyceride levels were between 500 and 2000 mg/dL were enrolled in these two studies of 6 and 16 weeks duration. The median triglyceride and LDL-C levels in these patients were 792 mg/dL and 100 mg/dL, respectively. Median HDL-C level was 23.0 mg/dL.

The changes in the major lipoprotein lipid parameters for the Lovaza and placebo groups are shown in Table 2.

Table 2: Median Baseline and Percent Change From Baseline in Lipid Parameters in Patients with Very High TG Levels (\geq 500 mg/dL)

| Parameter | LOVAZA N=42 | | Placebo N=42 | | Difference |
|-----------|----------------|----------|-----------------|----------|------------|
| | BL | % Change | BL | % Change | |
| TG | 816 | -44.9 | 788 | +6.7 | -51.6 |
| Non-HDL-C | 271 | -13.8 | 292 | -3.6 | -10.2 |
| TC | 296 | -9.7 | 314 | -1.7 | -8.0 |
| VLDL-C | 175 | -41.7 | 175 | -0.9 | -40.8 |
| HDL-C | 22 | +9.1 | 24 | 0.0 | +9.1 |
| LDL-C | 89 | +44.5 | 108 | -4.8 | +49.3 |

BL = Baseline (mg/dL); % Chg = Median Percent Change from Baseline; Difference = Lovaza Median % change - Placebo Median % Change

Lovaza 4 g per day reduced median TG, VLDL-C, and non-HDL-C levels and increased median HDL-C from baseline relative to placebo. Lovaza treatment to reduce very high TG levels may result in elevations in LDL-C and non-HDL-C in some individuals. Patients should be monitored to ensure that the LDL-C level does not increase excessively.

The effect of Lovaza on the risk of pancreatitis in patients with very high TG levels has not been evaluated.

The effect of Lovaza on cardiovascular mortality and morbidity in patients with elevated TG levels has not been determined.

INDICATIONS AND USAGE

Very High Triglycerides

Lovaza is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (\geq 500 mg/dL) triglyceride levels.

Usage Considerations:

In individuals with hypertriglyceridemia (HTG), excess body weight and excess alcohol intake may be important contributing factors and should be addressed before initiating any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, (such as hypothyroidism or diabetes mellitus) should be looked for and adequately treated. Estrogen therapy, thiazide diuretics, and beta blockers are sometimes associated with massive rises in plasma TG levels. In such cases, discontinuation of the specific etiologic agent, if medically indicated, may obviate the need for specific drug therapy for HTG.

The use of lipid-regulating agents should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use lipid-regulating agents, the patient should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet (See PRECAUTIONS).

CONTRAINDICATIONS

Lovaza is contraindicated in patients who exhibit hypersensitivity to any component of this medication.

PRECAUTIONS

General:

Initial Therapy: Laboratory studies should be performed to ascertain that the patient's TG levels are consistently abnormal before instituting Lovaza therapy. Every attempt should be made to control serum TG levels with appropriate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes mellitus and hypothyroidism) that may be contributing to the patient's TG abnormalities. Medications known to exacerbate HTG (such as beta blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG-lowering drug therapy.

Continued Therapy: Laboratory studies should be performed periodically to measure the patient's TG levels during Lovaza therapy. Lovaza therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment.

Information for Patients:

Lovaza should be used with caution in patients with known sensitivity or allergy to fish. Patients should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet.

Laboratory Tests:

In some patients, increases in alanine aminotransferase (ALT) levels without a concurrent increase in aspartate aminotransferase (AST) levels were observed. Alanine aminotransferase levels should be monitored periodically during Lovaza therapy.

In some patients, Lovaza increased low-density lipoprotein cholesterol (LDL-C) levels. As with any lipid-regulating product, LDL-C levels should be monitored periodically during Lovaza therapy.

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Drug Interactions:

Anticoagulants: Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of Lovaza and concomitant anticoagulants. Patients receiving treatment with both Lovaza and anticoagulants should be monitored periodically.

HMG-CoA reductase inhibitors: In a 14-day study of 24 healthy adult subjects, daily co-administration of simvastatin 80 mg with Lovaza 4 g did not affect the extent (AUC) or rate (C_{max}) of exposure to simvastatin or the major active metabolite, beta-hydroxy simvastatin at steady state.

Cytochrome P450-Dependent Monooxygenase Activities: Omega-3-fatty acid containing products have been shown to increase hepatic concentrations of cytochrome P450 and activities of certain P450 enzymes in rats. The potential of Lovaza to induce P450 activities in humans has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a rat carcinogenicity study with oral gavage doses of 100, 600, 2000 mg/kg/day by oral gavage, males were treated with omega-3-acid ethyl esters for 101 weeks and females for 89 weeks without an increased incidence of tumors (up to 5 times human systemic exposures following an oral dose of 4 g/day based on a body surface area comparison). Standard lifetime carcinogenicity bioassays were not conducted in mice.

Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or human lymphocytes. Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay.

In a rat fertility study with oral gavage doses of 100, 600, 2000 mg/kg/day, males were treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and throughout mating, gestation and lactation. No adverse effect on fertility was observed at 2000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. It is unknown whether Lovaza can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Lovaza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 g/day based on a body surface area comparison.

In female rats given oral gavage doses of 100, 600, 2000 mg/kg/day beginning two weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison).

In pregnant rats given oral gavage doses of 1000, 3000, 6000 mg/kg/day from gestation day 6 through 15, no adverse effects were observed (14 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

In pregnant rats given oral gavage doses of 100, 600, 2000 mg/kg/day from gestation day 14 through lactation day 21, no adverse effects were seen at 2000 mg/kg/day (5 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3000 mg/kg/day (7 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

In pregnant rabbits given oral gavage doses of 375, 750, 1500 mg/kg/day from gestation day 7 through 19, no findings were observed in the fetuses in groups given 375 mg/kg/day (2 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

Nursing Mothers:

It is not known whether omega-3-acid ethyl esters are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lovaza is administered to a woman who is breastfeeding.

Pediatric Use:

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric Use:

A limited number of patients over 65 years of age were enrolled in the clinical studies. Safety and efficacy findings in subjects over 60 years of age did not appear to differ from those of subjects less than 60 years of age.

ADVERSE REACTIONS

Treatment-emergent adverse events reported in at least 1% of patients treated with Lovaza 4 g per day or placebo during 8 randomized, placebo-controlled, double-blind, parallel-group studies for HTG are listed in Table 3. Adverse events led to discontinuation of treatment in 3.5% of patients treated with Lovaza and 2.6% of patients treated with placebo.

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Table 3: Adverse Events in Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Studies for Very High TG Levels (≥ 500 mg/dL) that Used LOVAZA 4 g per Day

| BODY SYSTEM Adverse Event | LOVAZA (N = 226) | | Placebo* (N = 228) | |
|--|---------------------|------|-----------------------|------|
| | n | % | n | % |
| Subjects with at least 1 adverse event | 80 | 35.4 | 63 | 27.6 |
| Body as a whole | | | | |
| Back pain | 5 | 2.2 | 3 | 1.3 |
| Flu syndrome | 8 | 3.5 | 3 | 1.3 |
| Infection | 10 | 4.4 | 5 | 2.2 |
| Pain | 4 | 1.8 | 3 | 1.3 |
| Cardiovascular | | | | |
| Angina pectoris | 3 | 1.3 | 2 | 0.9 |
| Digestive | | | | |
| Dyspepsia | 7 | 3.1 | 6 | 2.6 |
| Erectation | 11 | 4.9 | 5 | 2.2 |
| Skin | | | | |
| Rash | 4 | 1.8 | 1 | 0.4 |
| Special senses | | | | |
| Taste perversion | 6 | 2.7 | 0 | 0.0 |

Adverse events were coded using COSTART, version 5.0. Subjects were counted only once for each body system and for each preferred term.

*Placebo was corn oil for all studies.

Additional adverse events reported by 1 or more patients from 22 clinical studies for HTG are listed below:

BODY AS A WHOLE: Enlarged abdomen, asthenia, body odor, chest pain, chills, suicide, fever, generalized edema, fungal infection, malaise, neck pain, neoplasm, rheumatoid arthritis, and sudden death.

CARDIOVASCULAR SYSTEM: Arrhythmia, bypass surgery, cardiac arrest, hyperlipemia, hypertension, migraine, myocardial infarct, myocardial ischemia, occlusion, peripheral vascular disorder, syncope, and tachycardia.

DIGESTIVE SYSTEM: Anorexia, constipation, dry mouth, dysphagia, colitis, fecal incontinence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, intestinal obstruction, melena, pancreatitis, tenesmus, and vomiting.

HEMATOLOGIC-LYMPHATIC SYSTEM: Lymphadenopathy.

INFECTIONS AND INFESTATIONS: Viral infection.

METABOLIC AND NUTRITIONAL DISORDERS: Edema, hyperglycemia, increased ALT, and increased AST.

MUSCULOSKELETAL SYSTEM: Arthralgia, arthritis, myalgia, pathological fracture, and tendon disorder.

NERVOUS SYSTEM: Central nervous system neoplasia, depression, dizziness, emotional lability, facial paralysis, insomnia, vasodilatation, and vertigo.

RESPIRATORY SYSTEM: Asthma, bronchitis, increased cough, dyspnea, epistaxis, laryngitis, pharyngitis, pneumonia, rhinitis, and sinusitis.

SKIN: Alopecia, eczema, pruritus, and sweating.

SPECIAL SENSES: Cataract.

UROGENITAL SYSTEM: Cervix disorder, endometrial carcinoma, epididymitis, and impotence.

DRUG ABUSE AND DEPENDENCE

Lovaza does not have any known drug abuse or withdrawal effects.

OVERDOSAGE

In the event of an overdose, the patient should be treated symptomatically, and general supportive care measures instituted, as required.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving Lovaza, and should continue this diet during treatment with Lovaza. In clinical studies, Lovaza was administered with meals.

The daily dose of Lovaza is 4 g per day. The daily dose may be taken as a single 4-g dose (4 capsules) or as two 2-g doses (2 capsules given twice daily).

HOW SUPPLIED

Lovaza (omega-3-acid ethyl esters) capsules are supplied as 1-gram transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation REL900 in bottles of 60 (NDC 65726-425-15) and 120 (NDC 65726-425-27).

Recommended Storage:

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Do not freeze. Keep out of reach of children.

Rx only

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